Reduction of Serum Uric Acid in Young Men During Physical Training

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The effects of eight weeks of chronic physical exercise (training) on serum sodium urate concentration were investigated. Thirty normal, healthy male college students, aged 18 to 29, comprised the sample. Ten students were extremely active (athletic group), 10 were moderately active participants in a physical education class (training group) and 10 were relatively sedentary (control group). Serum sodium urate concentration and a physical fitness index (modified Harvard step test) were measured at the beginning, periodically during an eight week training period and after a four week "deconditioning" period.

Pre-experimental correlation coefficients between serum uric acid levels and age, height, weight, body surface area, resting heart rate and fitness index were low (0.003 to 0.214) and not significant statistically.

It was also found that chronic physical exercise lowered serum uric acid 0.3 to 3.2 mg/100 ml in 80 percent of the subjects in the athletic and training groups, particularly in those healthy persons with values of 7.0 to 8.5 mg/100 ml.

The most important finding of this study was a significant ($P < 0.05$) decrease in serum sodium urate concentration in the members of the athletic group, who underwent an extremely strenuous conditioning program compared to members of the other groups.

Probable mediating physiologic mechanisms are discussed to explain this finding. Practical implications are also discussed in view of the association between serum uric acid, gout and coronary artery disease and the uncertain effect of chronic exercise (training) on serum sodium urate concentration.

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The association of serum sodium urate concentration with gout has been known for many years, but more recently hyperuricemia has been observed to be associated with hypertension,[1,2] coronary artery disease,[3–5] essential hypercholesterolemia[6] and hypertriglyceridemia[7] with much greater frequency than in the general population.

Previous studies have indicated that acute exercise lasting between one-half and three hours elevates serum sodium urate levels approximately in proportion to the intensity of the exercise, with a maximal increase of 2.7 mg/100 ml.[8–11] The mechanism of this rise during the exercise appears to be associated with reduced renal plasma flow, perhaps mediated by increased sodium lactate production.[10]

Recently, a study of high school athletes not at peak training revealed elevated serum sodium urate values.[12] Medical examination of a group of 29 healthy male college athletes showed that an unexpected number (more than 50 percent) had serum sodium urate concentrations of 6.0 mg/100 ml or greater. This percentage was signifi-

TABLE I

Experimental Protocol for a Typical Subject

Pre-Experimental Measures (Week 1)	Experimental Measures (Weeks 2–10)	Post-Experimental Measures (Week 14)
Oct. 1–3 Dietary analysis	Oct. 17 SSUC	Jan. 9 SSUC
	Oct. 18 Step test	Jan. 10 Step test
Oct. 3 SSUC		
	Oct. 24 SSUC	Jan. 11 SSUC
Oct. 4 Step test (discarded)	Oct. 25 Step test	Jan. 12 Step test
Oct. 5 SSUC	Nov. 7 SSUC	
Oct. 6 Step test	Nov. 8 Step test	
	Dec. 12 SSUC	
	Dec. 13 Step test	

SSUC = serum uric acid concentration.

cantly higher, statistically, than the average value for this age group in the normal population.[13] One factor that could have contributed to those high values was participation in chronic physical exercise (training). Two other factors that might also have been implicated were genetic predisposition and achievement-oriented behavior and "drive,"[14,15] a factor certainly present in most athletes.

The question then arises whether the effects of acute and chronic exercise on serum urates are essentially identical. To our knowledge, there are only three previous studies that measured serum uric acid during longitudinal physical training.[16–18] When Marine recruits were investigated, serum uric acid levels were elevated an average of 0.2 mg/100 ml in the first study and decreased an average of 1.5 mg/100 ml in the second at the end of the training period. These changes are within the range of normal variation. One possible complicating factor was that these recruits were eating over 5,000 kcal/day, and the diets were rather high (45 percent) in saturated fat.[16,17] In the third study Rahe and Arthur[18] noted a decrease in serum urate levels during training and an increase during a period of great psychological stress.

In view of (1) the association between serum uric acid, gout and coronary artery disease, (2) the growing tendency of physicians to prescribe graded physical exercise as both a preventive measure[19] and a rehabilitation procedure[20] for patients who have had heart attacks, and (3) the uncertain role of chronic exercise on serum uric acid, the present study was undertaken to investigate the effect of eight weeks of chronic physical exercise (training) on serum sodium urate concentration.

Procedures and Methods

Procedures

This study was divided into three time periods: (1) a pre-experimental period, (2) an experimental (training) period, and (3) a post-experimental period (Table I).

Thirty college men, aged 18 to 29 years (mean 20.1), were studied for three and a half months. Reference data, including a diet analysis, are presented in Table II. The athletic group consisted of 10 athletes in training, the training group consisted of 10 members of a soccer class and the control group consisted of 10 members of a bowling class. Analysis of personal and family medical histories revealed that, with 1 exception, the subjects were normal healthy college students; 1 subject had only one kidney. Specifically, there was no personal history of medical conditions, drug or dietary habits that could affect serum urate nor was there any family history of such medical conditions.

After the pre-experimental measures (week 1), the exercise training period (experimental period weeks 2 to 10) continued for approximately eight weeks. The post-experimental measures (week 14) were taken approximately one month after cessation of training. During the pre- and post-experimental periods, the serum urate value was averaged from two samples taken two days apart. During the experimental (training) period, single serum urate determinations were performed during weeks 2, 3, 5 and 10. Change in overall physical fitness was estimated with a modified version of the Harvard step test.[21] Thereafter, a step test was given the day after each blood sample was obtained (Table I).

Training procedures: During the experimental period the athletic group underwent intensive two-hour daily physical conditioning sessions of sprint swimming, resistive exercises, water polo skill drills and weekly interschool competition. The subjects from the soccer class participated in a moderate exercise program consisting of (1) a daily one-mile run, (2) one hour of soccer a week, and (3) one-half hour of circuit training twice a week, consisting of muscular endurance exercises for the back, abdomen, legs, arms and shoulder girdle. The control group had two one-half hour bowling sessions a week, participated in little or no organized physical activity and led rel-

TABLE II
Subject Reference Data and Dietary Analysis

	Age (yr)	Height (cm)	Wt (kg)	DuBois Surface Area (m^2)	kcal	kcal/kg	Protein			Carbohydrates		Fat	
							g	%	g/kg	g	%	g	%
Athletic group													
Mean	19.5	186.6	81.2	2.07	3234.0	402.6	133.7	21.9	1.67	320.5	52.0	164.3	26.2
±SE	0.5	2.0	3.0	0.05	187.5	25.1	9.4	1.1	0.12	20.8	1.9	11.7	1.0
no.	10	10	10	10	30	30	30	30	30	30	30	30	30
Training group													
Mean	21.1	179.2	75.6	1.94	2384.2	313.8	118.2	26.1	1.54	221.2	48.8	114.6	25.1
±SE	1.1	2.5	3.4	0.05	127.3	15.3	7.6	1.1	0.08	14.9	1.6	8.0	1.2
no.	10	10	10	10	30	30	30	30	30	30	30	30	30
Control group													
Mean	19.8	181.8	70.8	1.91	2130.2	305.0	101.6	24.7	1.48	205.9	49.2	107.3	26.1
±SE	0.2	1.4	2.0	0.03	120.0	18.8	8.7	1.4	0.13	16.0	2.6	7.6	1.7
no.	10	10	10	10	27	27	27	27	27	27	27	27	27

atively sedentary college lives. The relative intensity of these programs indicated that (in terms of estimated caloric expenditure) the athletic group's program was about six times more vigorous than that of the training group and about 25 times more vigorous than that of the control group.

Methods

Diet: A three-day normal dietary intake was obtained from each subject during the pre-experimental period, and the content (Table II) was calculated from standard food tables.[22] The subjects were requested to eat normally during the experiment but to refrain from eating foods of high purine content (a list of these foods was given to each subject).

Uric acid analysis: The evening before blood samples were taken, the subjects were requested to eat a light dinner, to take no stimulants or medication and to sleep at least eight hours. Blood (5 to 7 ml) was drawn between 8 and 10 AM with the subjects in a post-absorptive condition. The serum was frozen and analyzed subsequently for uric acid with the carbonate-phosphotungstate method of Henry et al.[23] Control sera were analyzed concomitantly at each determination. One or two weeks elapsed between serum collection and uric acid analysis. The means ± standard deviations of 10 analyses each on serum samples taken from 2 subjects were 6.45 ± 0.05 and 5.68 ± 0.09 mg/100 ml; thus, the precision of the analytical technique was less than 0.1 mg/100 ml. The standard deviation of the differences between the two serum uric acid samples taken two days apart in the pre-experimental period was ± 0.5 mg/100 ml, representing the day to day subject variability plus the analytical error.

Physical fitness measurement: During the Harvard step test the subjects stepped up and down on a 45.7 cm (18 inch) bench at a rate of 120 count/min for three minutes. Then recovery heart rate (stethoscope) was taken at one to one and a half, two to two and a half and three to three and a half minutes after exercise. A fitness index was calculated according to Brouha et al.[21]

Statistical methods: Pre-experimental correlation coefficients were computed comparing serum uric acid, age, fitness index and body height, weight and surface area with data obtained from all subjects combined (no. = 30). Combined correlation coefficients for the pre-experimental, experimental and post-experimental periods were computed comparing only serum uric acid concentration and fitness index from all test data (no. = 180).

A univariate, repeated measures analysis of variance method was used to determine intragroup and intergroup differences during all periods. The level of significance used was $P \leq 0.05$, and nonsignificant differences are indicated by n.s. Since the greatest interest was in comparing the uric acid concentration between groups, the changes in uric acid concentration over time, and the interaction between these two effects, it was decided to use Scheffé's method[24] of multiple comparison.

Results

Uric acid: There was an average decrease in serum uric acid in the athletic group (Fig. 1) from 6.5 in week 1 to 5.2 mg/100 ml in week 10 ($P < 0.05$). There was an average decrease in serum uric acid in the training group from 6.4 to 6.0 mg/100 ml (n.s.) and an average decrease in the control group from 5.6 to 5.2 mg/100 ml (n.s.) during the same period of time. The average values in the athletic and training groups in the pre-experimental period were essentially equal, 6.5 and 6.4 mg/100 ml, respectively; those of the control group averaged 5.6 ml. None of the intergroup differences was significant statistically.

During the post-experimental period (weeks 10 to 14) the athletes' average uric acid rose from 5.2 to 6.0 mg/100 ml (n.s.), and the values for the training and control groups were essentially unchanged.

There were rather large individual differences in pre-experimental uric acid values (Fig. 2). The highest pre-experimental level in the control group was 6.6 mg/100 ml. In the training group 1 subject had a

pre-experimental uric acid level of 8.4 mg/100 ml that was reduced to 6.5 by week 10 and remained there during the post-experimental period. The three highest pre-experimental uric acid values in the athletic group were reduced by 2.3, 3.2 and 0.8 mg/100 ml, respectively, at the end of the experimental period. During the post-experimental period, one of these values remained low while the other two rose again. In the athletic group, during the experimental (training) period, only 1 subject had an increase in uric acid (0.4 mg/100 ml); the other 9 had decreases of 0.5 to 3.2 mg/100 ml. The greatest decrease was in the subject with only one kidney.

In the training group, during the experimental period, 3 subjects had increases in serum uric acid of 0.1 to 0.2 mg/100 ml; the other 7 had decreases of 0.3 to 1.9 mg/100 ml. Changes in the control group ranged from +0.3 to −1.4 mg/100 ml during the experimental period. Pre-experimental correlation coefficients, comparing uric acid, fitness index, body surface area, weight, height and age from data obtained from all subjects combined (no. = 30) ranged from −0.003 to +0.214 (n.s.). Combined correlation coefficients (no. = 180) for all three periods ranged from −0.109 to +0.025 (n.s.).

The uric acid results may be summarized as follows:

1. During the pre-experimental period, average uric acid concentrations were essentially the same (6.4 and 6.5 mg/100 ml) in the athletic and training groups. Average concentrations were higher in the athletic and training groups than in the control group (5.6 mg/100 ml), but none of the intergroup differences was significant statistically.

2. During the experimental period uric acid decreased in the athletic group from 6.5 to 5.2 mg/100 ml ($P < 0.05$); in the training group from 6.4 to 6.0 mg/100 ml (n.s.) and in the control group from 5.6 to 5.2 mg/100 ml (n.s.).

3. During the post-experimental period the average uric acid increased toward the pre-experimental levels only in the athletic group (n.s.).

4. Correlation coefficients comparing uric acid and fitness index, body surface area, weight, height and age were low (n.s.) indicating little, if any, influence of these variables upon uric acid.

Fitness index: Contrary to the uric acid values in the pre-experimental period, the fitness indexes in the training and control groups (Fig. 1) were the same, but the index in the athletic group was significantly higher ($P < 0.05$) than that in either of the other two groups. The athletes' fitness index rose somewhat up to week 5 of the experimental period but then fell to below the pre-experimental level by week 10. The fitness index continued to fall during the post-experimental period, and this decline was expected to accompany the cessation of training.

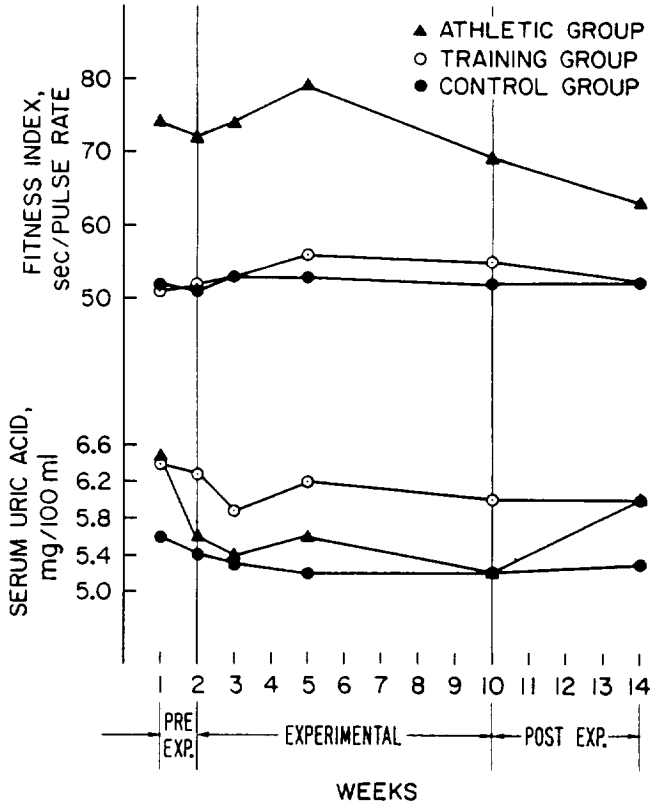

Figure 1. *Average values for the fitness index and serum uric acid concentration* in the three experimental groups during pre-experimental, experimental and post-experimental periods.

The training procedures during the experimental period appeared to raise the fitness index of the training group slightly (n.s.) above that of the control group but it returned to the pre-experimental level by the end of the post-experimental period. These results indicate that the nature or the intensity, or both, of the training group's exercise program was not sufficient to alter appreciably the fitness index. However, the average times for a one-mile run by 7 of the 10 training group subjects did improve from 7.66 ± 0.77 min. to 6.75 ± 0.61 min. during the experimental period ($P < 0.001$).

Anthropometric and dietary measures: Analysis of anthropometric measures obtained during the pre-experimental period (Table II) indicated that members of the athletic group were taller ($P < 0.05$) than members of the training and control groups and heavier ($P < 0.05$) than members of the control group. No significant pre-experimental intergroup differences were found in body surface area, age and uric acid.

The results of the pre-experimental dietary analysis are also found in Table II. The members of both the athletic and training groups ate slightly more protein (total grams and grams/body weight) than members of the control group.

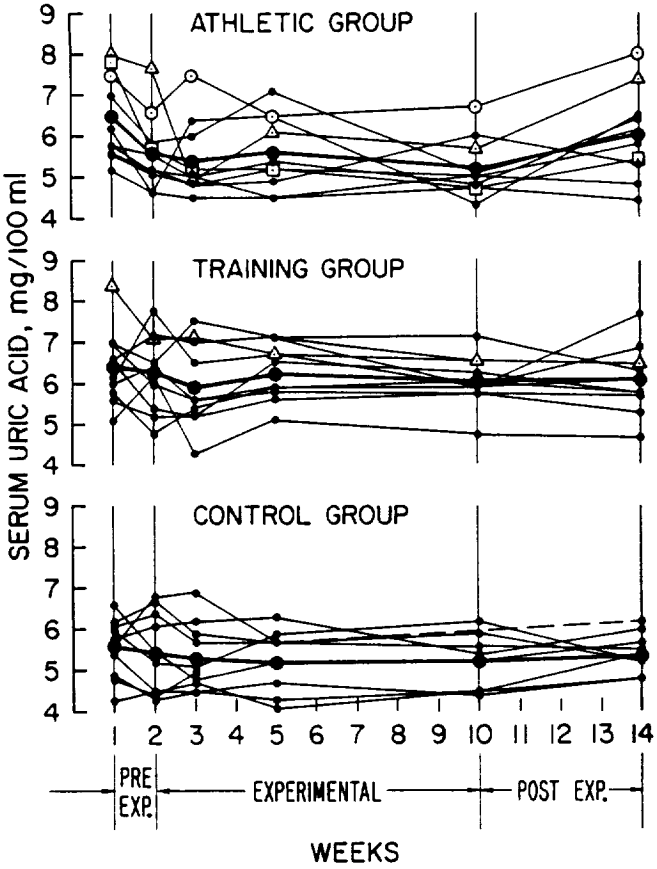

Figure 2. *Individual values for serum uric acid concentration in three experimental groups* during pre-experimental, experimental and post-experimental periods. Subjects with pre-experimental serum uric acid levels above 7.0 mg/100 ml are denoted with different symbols. The heavy line represents the average value for that particular group.

Discussion

Pre-experimental period: The dissociation between the three groups in levels of uric acid and the fitness index points to the independence of the two variables. The fitness of the training group was the same as that of the control group, but the training group's average serum uric acid was the same as that of the athletes. It appears we were dealing with two distinct populations, one (athletic and training groups) exhibiting more physical "drive" and the other (control group) less "drive." Other recent studies have indicated positive statistical association of high uric acid levels and high levels of "drive," achievement, and leadership.[4,14,15,25] Montoye et al.[12] observed that high-school athletes had resting serum uric acid levels significantly higher than those of non-athletes, but athletes "in-season" had a uric acid value 0.6 mg/100 ml lower than "out-of-season" values, thus suggesting that increased activity was associated with lower concentrations of uric acid. In another study Montoye et al.[4] observed in a group of business executives a direct relation between physical activity and serum uric acid levels: The uric acid concentration of the most active group averaged 6.50 mg/100 ml, and average for the least active group was 5.80 mg/100 ml. Thus, there seems to be a paradoxical relation between level of activity and concentration of uric acid. This discrepancy can be resolved if we assume the activity levels of relatively sedentary people, such as executives, are more closely dependent upon a "drive"-achievement factor; hence, the higher uric acid. This would also explain why athletes have higher uric acid levels when out of training; a "drive"-hereditary factor "sets" the resting level, but chronic exercise (training) decreases the uric acid. The increase in uric acid values in the athletes in the present study during the post-experimental period further supports this hypothesis.

Experimental period: The significant decrease in serum uric acid in the athletes compared with the smaller decrease in the training group appeared to be related to the intensity of the training procedures. Factors that could have contributed to the lowering of the uric acid with exercise training can be classified under (1) primary effects on uric acid metabolism per se due to the exercise stimuli, and (2) secondary reactions of uric acid due to the effects of exercise on some other variable, such as lipid or amino acid metabolism.

The primary effects could include (a) a decrease in uric acid production with constant excretion; (b) an increased excretion with constant production; (c) no change in uric acid turnover rate, but a progressively increasing plasma volume during the experimental period; and (d) some influence of diurnal or seasonal variations, or both, on uric acid metabolism.

First, since strenuous exercise increases metabolic demands and cellular turnover, it is likely there would be an increase rather than a decrease in the quantity of purines and proteins added to the total pool which would tend to increase uric acid concentrations. The uric acid pool in the body averages about 1,200 mg with a range between 870 and 1,590 mg with a daily turnover of about 60 percent.[26] In the present study the subjects ate their normal diets, and since the athletic and training groups consumed slightly more dietary protein per kilogram of body weight than the control group, the result should be a tendency to *increase* the total urate pool.

Second, uric acid excretion has not been studied systematically during long-term exercise training. However, after single exertions serum uric acid rises 0.5 to 2.7 mg/100 ml,[8-11] depending upon the duration and intensity. After exercise, renal clearance of uric acid can be depressed to as low as 20 percent of the pre-exercise values but it returns to normal values in one to two hours after exercise.[10] Plasma volume decreases between 600 and 1,900 ml after rather strenuous acute exercise.[27] Assuming a plasma volume of 3,000 ml, no gain or loss of uric acid and a serum uric acid concentration of 6.4 mg/100 ml (192 mg), a

transference of only 900 ml of plasma from the blood vessels to the interstitial spaces would increase serum uric acid levels by 2.7 mg/100 ml. Thus, decreased renal clearance or plasma volume loss, or both, could account for the increased serum uric acid with acute exercise. In addition, many of the physiologic and metabolic changes resulting from acute exertion would tend to inhibit renal urate excretion: ketone bodies, particularly beta hydroxybutyrate and acetoacetate, retard urate clearance,[28] and lacticacidemia impairs uric acid excretion by a mechanism not dependent upon the lacticacidosis.[10] A decreased urinary flow, due mainly to a reduction in renal plasma flow during exercise[29] and accentuated by total body dehydration due to sweating, respiratory water loss and inhibition of voluntary water consumption,[30] would also retard uric acid excretion. However, all these mechanisms would act to *elevate* serum uric acid levels in conjunction with increased urate production during exercise training. As training continues, a compensatory increase in uric acid excretion, proportional to the intensity of the stress, may occur and result in an absolute lowering of serum uric acid levels. The main avenue would have to be through the renal system since the palmar and body sweat uric acid concentration is below 1.8 mg/100 ml.[31,32]

Third, it is possible that the progressively decreasing serum uric acid levels during the training period were due to a progressively increasing plasma volume with a relatively constant turnover rate of uric acid. Assuming an average plasma volume of 3,000 ml and a 20 percent increase with training to 3,600 ml,[33] then an initial serum uric acid concentration of 6.4 mg/100 ml in 3,000 ml would reduce to 5.3 mg/100 ml in 3,600 ml of plasma. The average uric acid of the athletes was 5.2 mg/100 ml at the end of the experimental period. Since members of the training group had a relatively easier training program it is possible that their increase in plasma volume was less; therefore, a smaller decrease in serum uric acid was observed.

Fourth, since the duration of the study was from October to January, it was possible for seasonal variations in serum uric acid and plasma volume to influence the results. There is no regular cyclic change in serum uric acid concentration that coincides with the seasons, although one study showed that uric acid concentration was constant in October and November but rose in December.[34] In the present study seasonal influences did not appear to play a significant role in the explanation of hypouricemia in the trained athletes.

Fifth, decreased serum uric acid in the athletic group might have been the secondary result of the decrease in some other primary factor resulting from chronic exercise stimuli. Some recent studies, but not all, have emphasized the positive relation between serum uric acid and various serum lipids, particularly cholesterol and triglycerides.[6,7,16,17,35,36] For example, in 100 patients with hypercholesterolemia the correlation coefficient between serum uric acid and triglyceride concentrations was 0.64,[7] but Benedek[37] found no significant positive correlation between uric acid and either cholesterol or triglyceride concentration in either men or women. An explanation of the failure of Calvy et al.[17,18] to find any appreciable decrease in uric acid with hard longitudinal training plus the high fat diet and increased triglyceride concentrations may be found in the studies of the inhibitory effects of the ketone bodies (mainly beta hydroxybutyrate and acetoacetate) on the renal clearance of urate.[27,38,39] The results of Calvy et al. suggest that serum uric acid does not respond to the exercise per se but is related to serum lipid concentrations, perhaps through ketone concentration.

The two most likely explanations of the significant lowering of serum uric acid during longitudinal exercise training observed in the present study are (1) a relatively constant turnover of urate but a progressively increasing plasma volume, and (2) an absolute increase in urinary uric acid excretion. The final answer must await further research.

Practical implications: It seems important that uric acid levels be maintained as low as possible because Hall et al.[3] found that among those subjects who had uric acid levels of 8.0 mg/100 ml or higher, 36 percent had gouty arthritis and among those who had uric acid levels above 9.0 mg/100 ml, 40 percent had renal calculi. Yü and Gutman[40] reported that among those subjects who had uric acid levels above 12 mg/100 ml, 50 percent had renal calculi.

The results of the present study indicate that longitudinal physical exercise lowered serum uric acid levels from 0.3 to 3.2 mg/100 ml in 80 percent of the subjects and particularly in those apparently healthy persons with values of 7.0 to 8.5 mg/100 ml. These results should not be extended to individuals with serum uric acid levels greater than 8.5 mg/100 ml.

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